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Microwave assisted synthesis of Isoflavones

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ABSTRACT

Isoflavones are phenolic natural products occur in nature in plants, they are secondary metabolites. They are molecules of flavonoid family. Isoflavones are derived from 3-phenylchromen-4-one. They possess diversified biological activities. Therefore, various organic/medicinal chemists around the world have developed various synthetic routes methodologies to achieve the target molecules. We wish to report here with a green approach. In our methodology Deoxy benzoin was obtained by treating a substituted phenol with phenyl acetic acid in presence of BF3etherate as a Lewis acid. This intermediate in presence of Vilsmeir reagent and DMF was cyclized under microwave to furnish the product in good yield.

Keywords: Flavonoids, Isoflavones, Biologically Active, Green Chemistry, Microwave

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INTRODUCTION

Isoflavones are phenolic natural products occur in nature in plants [1, 1a,1b,1c]. They are secondary metabolite. They are molecules of flavonoid family. They are found in cabbage, soybean and grains. Some examples of molecules of this family are daidezin, genistein, formonenitin and biochanin etc [2]. Isoflavones have wide spectrum biological activities like antioxidant [2], anti-osteoporotic [2] and hypolipidemic [2], estrogenic [3], antibacterial [4], anticancer [5], antimicrobial [6], antiulcer [7], protiens tyrosine kinase inhibitor [8] insecticidal[9]. The basic isoflavone skeleton is shown below,

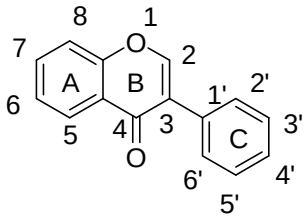


Figure1 :Basic skeleton of isoflavone

Some naturally occurring isoflavones with their structure is shown below,

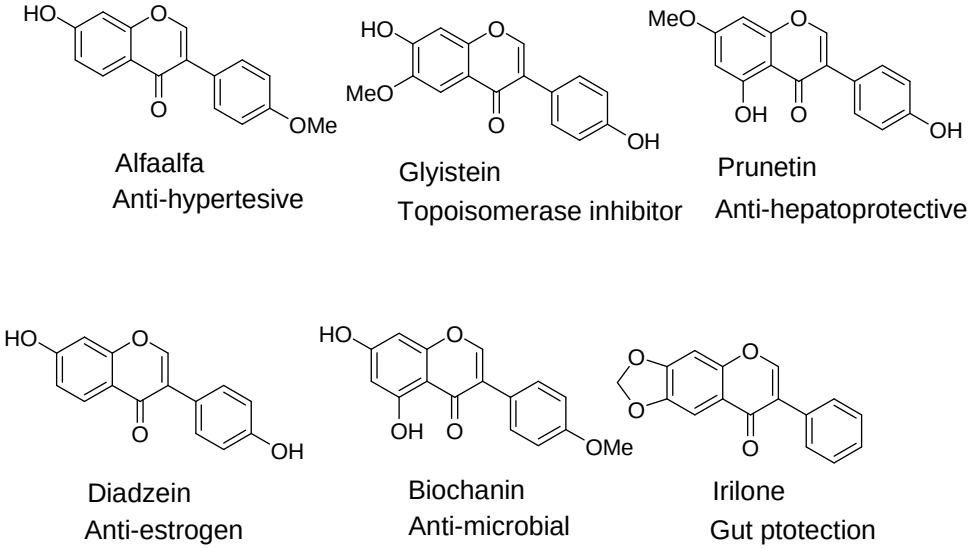
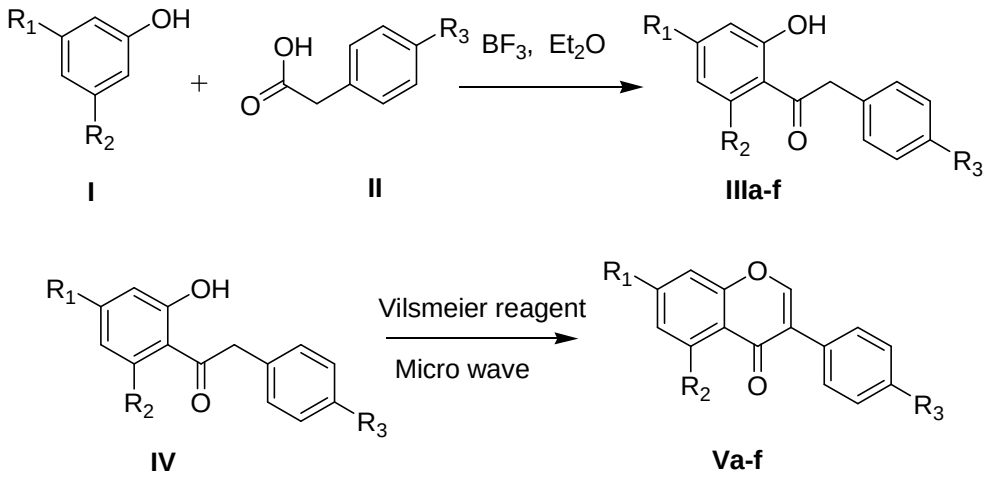


Figure2: Isoflavone with biological activity

Isoflavones are synthesized by traditional method through deoxybenzoin cyclization to give isoflavone [10,11].Therefore this deoxybenzoin is key intermediate in the synthesis of isoflavone. This intermediate treated with Vilsmeyer reagent to give corresponding isoflavone. The important pathways by different reagents includes ethoxalylchloride in pyridine[12], pyridine with triethylorthoformate [13], DMF/$POCl_3$ [14] or $MeSO_2Cl$ [15], anhydrous ethylformate and powdered sodium [16], acetic anhydride and sodium acetate [17, 18], acetic-formic unhydride [19], N-formylimidazole and THF [20], phenyliodine/trifluoroacetate [21] cyclization of deoxybenzoin. Another pathway includes oxidative rearrangement of chalcone using thallium acetate, thallium nitrate [22-31]. Also chalcone of epoxide followed by catalytic hydrogenation [32-33]. Some of well-known route includes conversion of flavanones into isoflavones by thallium nitrate in a mixture of methanol and chloroform [34], arylation of 4-chromanones in DMSO [35, 36], reaction of arylboronic acid with aryl chromanones using tetrakis(triphenylphosphine) palladium catalyst called coupling reaction[37]. Another important name reactions for the synthesis of isoflavone includes Bass et.al [38], Baker et. al. [39], Farkas et.al [40], Pelter and Foot [41] and Yoder et.al. [42]. All the reactions mentioned above are thermal and time consuming. We wish to report here with a green approach. In our methodology Deoxy benzoin was obtained by treating a substituted phenol with phenyl acetic acid in presence of BF_3etherate as a Lewis acid. This intermediate in presence of Vilsmeir reagent and DMF was cyclized under microwave to furnish the product in good yield. The reaction is depicted in scheme-1.

Scheme-1: Synthesis of Isoflavones by Vilsmeyer reagent under microwave method



Va: R_1=R_2=R_3=R_3 =H; Vb: R_1=R_2=R_3=OH;
Vc: R_1=OH, R_3= OMe; R_2=H; Vd: R_1=OH, R_3= OH; R_2=H
Ve: R_1=OMe, R_3= OMe; R_2=OH; Vf: R_1=OMe, R_3= H; R_2=H

EXPERIMENTAL SECTION

All the melting points reported are uncorrected and were recorded using an electro thermal melting point apparatus or with Buchhi melting point apparatus B-450. All the reagents purchased from Sigma Aldrich and Merck and used without further purification. Column chromatography purification was carried out using silica gel 60-120 and 230-400 mesh size and TLC was performed on E-Merck pre-coated silica gel 60 F254 plates and the spots were rendered visible by exposing to UV light or iodine. IR spectra were recorded on Brucker & Shimadzu FTIR instrument.^{1}HNMR spectra were recorded on Brucker 400 & 600 MHz ^{1}HNMR spectrometer. Spectrometers chemical shift (δ) reported are referred to internal reference Tetramethylsilane (TMS).The following abbreviations were used: s = singlet, d = doublet, dd = doublet of doublet, ddd doublet of doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, q = quintet, m = multiplet, bs = broad singlet. Micro-analytical data were obtained using Perkin Elmer 240Q elemental analyzer. Microwave oven used was LG microwave MOD-MG-1742WE, 2450MHz and 700 W maximum output.

General method for the synthesis of isoflavone

A mixture of substituted phenol (3 mmole), 2-phenyl acetic acid (3 mmole) was charged in RBF. Under nitrogen purging $BF_3{\cdot}Et_2O$ (15 mmol) was added in the same flask. Reaction mass was stirred at RT for 15 minute then refluxed at 90^0C for 1.5 hrs. under nitrogen purging. The reaction mass was cooled to 10^0C and DMF (4.6 ml) was added drop wise. The above reaction mixture was then added drop wise with stirring in to Vilsmeier reagent (4.5 mmol) at room temperature. The reaction mixture was stirred under microwave till completion of reaction (monitored by TLC). After completion of reaction the reaction mass was poured into boiling dilute HCl slowly and cooled. The solution was extracted with ethyl acetate (25 ml×3) and the organic layer was dried over anhydrous Na_2SO_4. The crude product obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform-methanol mixture as eluent to furnish the pure product. (**Va-f**).

Table 1: Isoflavones synthesized by Microwave assisted Vilsmeier reagent

Entry	R_1	R_2	R_3	Heat (time)	MW (time)	Yield (%)	M.P. (^{0}C)
Va	H	H	H	2.0 hrs	15 min	85	154[**Ref. 43,** 155^{0}C**]**
Vb	OH	OH	OH	2.5 hrs	30 min.	75	295[**Ref. 43,** 295^{0}C]
Vc	OH	H	OMe	2.5 hrs	25 min	84	257[**Ref. 43,** 258^{0}C]
Vd	OH	H	OH	2.5 hrs	20 min	81	323[**Ref. 43,** 320^{0}C]
Ve	OMe	OH	OMe	2.0 hrs	15 min	87	140[**Ref. 44,** 143^{0}C]
Vf	OMe	H	H	2.0 hrs	20 min	85	157[**Ref. 43,** 158^{0}C]

Spectral data of compounds:

3-phenyl-4H-chromen-4-one (Va)

Yield: 85%
Colour: pale yellow to white powder,
M.P.: 154^0C,
TLC system: hexane +E.A. (7.5+2.5),
Solubility: $CHCl_3$,

IR (KBr , cm^{-1}): 590-907 (aromatic region), 750 (ortho disub. benzene ring), 1212-1282(C-O, ether), 1472 & 1508-1600(C=C, aromatic), 1622(C=O, conjugated), 3000(aromatic, C-H)

^{1}HNMR (in CDCl3) δ_H = 8.039(s, 1H, C-2), 8.33 (dd,1H, J=7.2, 2.0 Hz, C-5), 7.46-7.46(m,1H, J=7.2, 2.0, 1.1 Hz, C-6), 7.68-7.71(m, 1H, J=7.2, 2.0, 1.1 Hz, C-7), 7.58 (d,1H, J=7.2Hz, C-8), 7.49-7.50(dd, 2H, J= 7.1, 2.1 Hz), 7.57-7.58(dd, 2H, J=7.1, 2.1Hz, C-3', C-5'), 7.38-7.40(t, 1H, J=7.1, 2.1, 1.1 Hz, C-4'). Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54 Found: C, 81.12; H, 4.67.

5, 7-dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one (Vb)

Yield: 75 %
Colour: pale yellow powder,
M.P.: 295^0C,
TLC system: $CHCl_3$ + MeOH (9+1),
Solubility: DMSO,

IR (KBr, cm^{-1}): 665-907 (aromatic region), 747 (ortho disub. benzene ring), 1245-1316 (C-O, ether), 1477 & 1551-1586 (C=C, aromatic), 1622(C=O, conjugated), 3003(aromatic, C-H), 3154 & 3449 (OH, phenolic).

^{1}HNMR (in DMSO) δ_H = 8.30(s, 1H, C-2), 6.21 (d,1H, J=2.0 Hz, C-6), 6.37(d, 1H, J=1.1 Hz, C-8), 7.36 (d, 2H, J=7.2 Hz, C-2', C-6'), 6.81 (d, 2H, J=7.2Hz, C-3'& C-5'), 9.8 (s, 1H, OH, C-4'), 10.9 (s, 1H, C-7), 12.9(s, 1H, C-5).Anal Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73 Found: C, 67.87; H, 3.67

7-hydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one (Vc)
Yield: 84 %
Colour: white powder,
M.P.: 257^{0}C,
TLC system: $CHCl_3$ + E.A. (9+1),
Solubility: DMSO,

IR (KBr, cm^{-1}): 614-887 (aromatic region), 780 (ortho disub. benzene ring), 1100-1252 (C-O, ether), 1454 & 1513-1605(C=C, aromatic), 1634(C=O, conjugated), 3073(aromatic, C-H), 3467 (OH, phenolic).

^{1}HNMR (in DMSO) δ_H = 8.30(s, 1H, C-2), 6.85-6.86 (dd,1H, J=7.5 , 1.3 Hz, C-5), 6.92-6.93(d, 1H, J=7.5,1.3 Hz, C-6), 7.95-7.96(d,1H, J=1.3 Hz, C-8), 7.48-7.50 (d, 2H, J=7.2 Hz, C-2',C-6'), 6.96-6.98 (d, 2H, J=7.2 Hz, C-3'& C-5'), 10.81 (s, 1H, OH,C-7), 3.77 (s, 1H, C-4').Anal. Calcd. for Chemical Formula: $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.79; H, 4.73.

7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one (Vd)
Yield: 84%
Colour: off white powder,
M.P.: 323^{0}C,
TLC system: $CHCl_3$ + E.A. (9+1),
Solubility: DMSO,

IR (KBr, cm^{-1}): 629-904 (aromatic region), 790 (ortho disub. benzene ring), 1110-1281 (C-O, ether), 1464 & 1515-1620(C=C, aromatic), 1654(C=O, conjugated), 3073(aromatic, C-H), 3212 (OH, phenolic, C-4'), 3471(OH, phenolic,C-7)

^{1}HNMR (in DMSO) δ_H = 8.28(s, 1H, C-2), 7.95 (d,1H, J=7.5 , C-5), 6.92(dd, 1H, J=7.50,1.5 Hz, C-6), 6.85(d,1H, J=1.5Hz), 7.37 (d, 2H, J=7.5 Hz, C-2',C-6'), 6.79 (d, 2H, J=7.5 Hz, C-3'& C-5'), 10.79 (s, 1H, OH, C-7), 9.53 (s, 1H, OH, C-4'). Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96.Found : C, 70.97; H, 4.06.

5-hydroxy-7-methoxy-3-(4-methoxyphenyl)-4H-chromen-4-one (Ve)
Yield: 87%
Colour: white powder,
M.P.: 140^{0}C,
TLC system: hexane + E.A. (9+1),
Solubility: $CHCl_3$,

IR (KBr, cm^{-1}): 656-911 (aromatic region), 764 (ortho disub. benzene ring), 1110-1285 (C-O, ether), 1475 & 1511-1598(C=C, aromatic), 1639(C=O, conjugated), 3073(aromatic, C-H), 3458 (OH, phenolic C-5).

^{1}HNMR (in $CDCl_3$) δ_H = 7.26(s, 1H, C-2), 6.40 (d,1H, J=7.5 , C-6), 7.86(weak d, 1H, J=1.5 Hz, C-8), 6.99 (d, 2H, J=7.5 Hz, C-2', C-6'), 7.47 (d, 2H, J=7.5 Hz, C-3'& C-5'), 12.9 (s, 1H, OH, C-5), 3.90 (s,1H, OMe, C-7), 3.80(s,1H, OMe, C-4'). Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.63; H, 4.91.

7-methoxy-3-phenyl-4H-chromen-4-one (Vf)
Yield: 85%
Colour: white powder,
M.P.: 157^{0}C,
TLC system: hexane + E.A. (7+2.5),
Solubility: $CHCl_3$,

IR (KBr, cm^{-1}): 664-949 (aromatic region), 866 (ortho disub. benzene ring), 1081-1296 (C-O, ether), 1570-1608(C=C, aromatic), 1644(C=O, conjugated), 3078(aromatic, C-H).

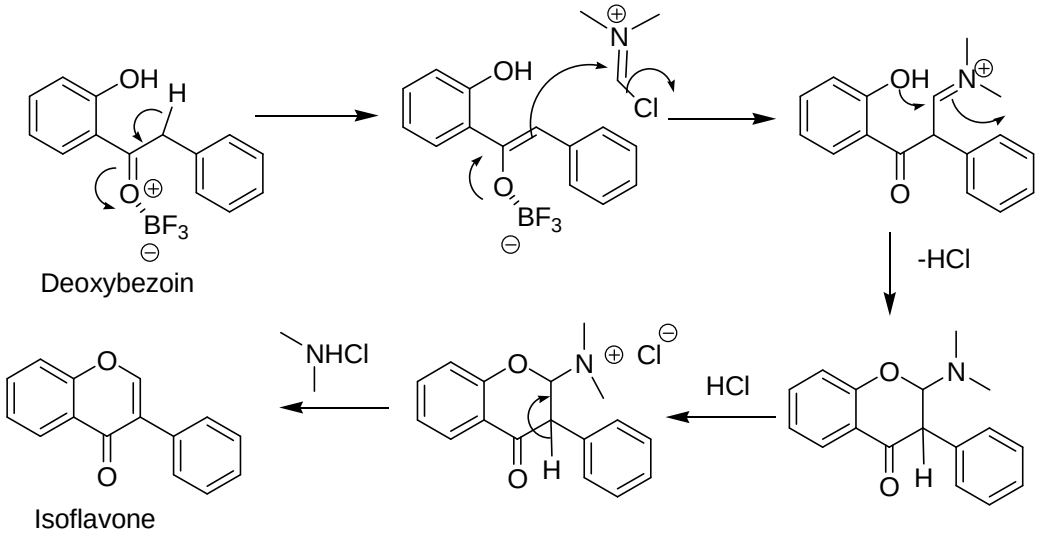
^{1}HNMR (in $CDCl_3$) δ_H = 7.95 (s, 1H, C-2), 3.9(3H, s, OH, C-7), 8.21-8.23(1H, d, J=7.5Hz, C-5), 6.86-6.87(1H, d, J=1.3 Hz,C-8), 6.99-7.01(1H, dd, J=7.5, 1.5Hz, C-6), 7.36-7.39(t, 2H, J=7.5, 1.5 Hz, C-2'& C-6'), 7.55-7.56(2H, d,

J=7.5Hz, C-3', C-5'), 7.42-7.45(1H, t, J=7.5,1.5 Hz). Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.38; H, 4.89.

RESULTS AND DISCUSSION

Isoflavones were synthesized using Vilsmeier reagent. In previous methods isoflavones were synthesized under thermal conditions. We wish to report here with a green approach. In our methodology Deoxy benzoin was obtained by treating a substituted phenol with phenyl acetic acid in presence of BF_3etherate as a Lewis acid. This intermediate in presence of Vilsmeir reagent and DMF was cyclized under microwave to furnish the product in good yield. Microwave is a green technology and increases speed of reaction. The molecules react faster under microwave condition. The possible mechanism for the reaction is depicted in following scheme-2.

Scheme-2 : Mechanism for the formation of isoflavone



All compounds purified by silica gel column chromatography. Structure of compounds conformed by IR and ^{1}HNMR spectroscopy followed by elemental analysis.

CONCLUSION

A new microwave assisted methodology is developed for the synthesis of isoflavones. This is a green approach the reaction time is reduced with good yield of the product

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